

# How plants LINC the SUN to KASH

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**Keywords:** nuclear envelope, LINC complex, SUN, KASH, plant, *Arabidopsis*

**Abbreviations:** CCSD, canonical C-terminal SUN domain; ER, endoplasmic reticulum; INM, inner nuclear membrane; KASH, Klarsicht/ANC-1/Syne homology; LINC, linkers of the nucleoskeleton to the cytoskeleton; NE, nuclear envelope; ONM, outer nuclear membrane; PM3, plant-prevalent mid-SUN 3 transmembrane; SUN, Sad1/UNC-84

Linkers of the nucleoskeleton to the cytoskeleton (LINC) complexes formed by SUN and KASH proteins are conserved eukaryotic protein complexes that bridge the nuclear envelope (NE) via protein-protein interactions in the NE lumen. Revealed by opisthokont studies, LINC complexes are key players in multiple cellular processes, such as nuclear and chromosomal positioning and nuclear shape determination, which in turn influence the generation of gametes and several aspects of development. Although comparable processes have long been known in plants, the first plant nuclear envelope bridging complexes were only recently identified. WPP domain-interacting proteins at the outer NE have little homology to known opisthokont KASH proteins, but form complexes with SUN proteins at the inner NE that have plant-specific properties and functions. In this review, we will address the importance of LINC complex-regulated processes, describe the plant NE bridging complexes and compare them to opisthokont LINC complexes.

The nuclear envelope (NE) is a double membrane system consisting of an inner nuclear membrane (INM) and an outer nuclear membrane (ONM). Studies in opisthokonts revealed that the two membranes are bridged by protein complexes formed by the INM Sad1/UNC-84 (SUN) proteins and the ONM Klarsicht/ANC-1/Syne homology (KASH) proteins.<sup>1–3</sup> SUN-KASH complexes have been found from yeast to humans, and they serve as linkers of the nucleoskeleton or chromosomes to the cytoskeleton (LINC) complexes.<sup>4–7</sup> LINC complexes regulate nuclear shape, rigidity and position of the nucleus as well as chromatin organization. The recent identification of a plant NE-bridging complex showed that it has plant-specific properties and functions.<sup>8</sup> Here we will briefly review opisthokont LINC complexes and then focus on novel insights on plant NE-bridging proteins.

## Opisthokont SUN and KASH Proteins

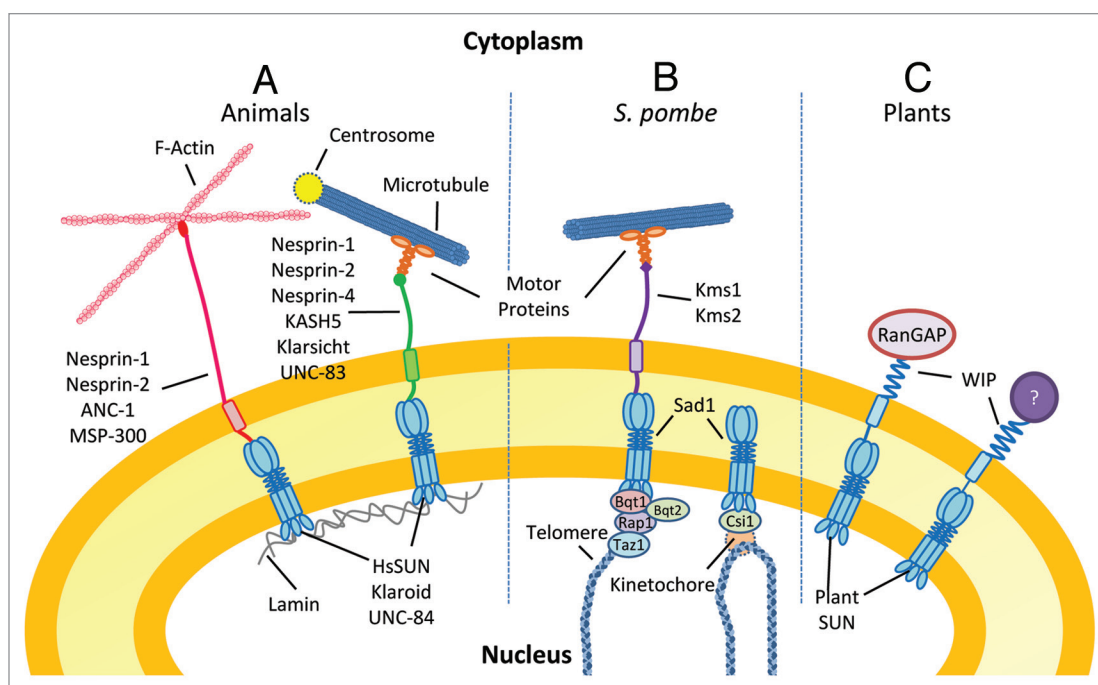
The founding member of SUN proteins is *Caenorhabditis elegans* UNC-84. The C-terminus of UNC-84 has a domain sharing homology with two human proteins and *Schizosaccharomyces*

*pombe* Sad1, a component of the spindle pole body.<sup>9</sup> This domain was subsequently found to interact with a C-terminal domain conserved in a series of ONM proteins including Klarsicht, ANC-1, and Syne (also known as Nesprin).<sup>10</sup> Therefore, the two interacting domains were named Sad1/UNC-84 (SUN) domain<sup>9</sup> and Klarsicht/ANC-1/Syne homology (KASH) domain,<sup>10</sup> respectively. SUN proteins typically locate at the INM with their C-terminal SUN domain positioned in the perinuclear space (PNS) (Fig. 1 and see below). KASH proteins are tail-anchored proteins at the ONM harboring a C-terminal KASH domain, which contains a short PNS tail (~30 amino acids) typically ending with a PPPX (X represents any amino acid) motif that is essential for interacting with the SUN domain. The SUN-KASH complexes bridge their binding partners across the NE (Fig. 1). In the nucleoplasm, the N-termini of many SUN proteins interact directly or indirectly with nuclear lamins, which are intermediate filament proteins located underneath the INM and are considered components of the nucleoskeleton.<sup>11</sup> At the cytoplasmic side, KASH proteins are linked to motor proteins, intermediate filaments, microtubules, or F-actin.<sup>4–7,12</sup>

Mammalian SUN1 and SUN2 interact with lamin A, and the NE localization of SUN2 depends on lamin A.<sup>13,14</sup> SUN1 and SUN2 interact with the mammalian KASH proteins nesprin-1 and nesprin-2 at the NE.<sup>4,15,16</sup> These two KASH proteins consist of N-terminal F-actin-binding calponin homology domains, a long stalk domain composed of spectrin repeats, and a C-terminal KASH domain.<sup>4,16</sup> The spectrin repeats each assemble into a three-helix bundle, which makes the protein flexible in length and may assist in buffering against mechanical stress.<sup>17</sup> Nesprin-1 and -2 interact with F-actin and connect the INM lamins through SUN1 and SUN2 (Fig. 1A).<sup>4,18</sup> These LINC complexes are responsible for anchoring the synaptic nuclei at the mouse neuromuscular junction.<sup>18</sup> Nesprin-1 and -2 also link the centrosome to the nucleus through interactions with the dynein-dynactin complex (Fig. 1A).<sup>19</sup> This connection is essential for interkinetic nuclear migration and nucleokinesis in mice.<sup>19</sup>

In *Drosophila*, the localization of Klarsicht at the nuclear periphery depends on a type B lamin and a SUN protein, klaroid.<sup>20</sup> Klaroid also forms nuclear aggregates in transgenic flies expressing a mutated lamin C that lacks the first 42 amino acids,<sup>21</sup> suggesting that klaroid might be associated with lamin C. Klarsicht is connected to microtubules and is responsible for the apical nuclear migration during photoreceptor formation.<sup>20,22</sup>

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**Figure 1.** Nuclear envelope bridging complexes in different organisms. Since SUN domains are relatively conserved across species, all SUN proteins are drawn as trimers according to the evidence provided for HsSUN2.<sup>39,40</sup> For simplicity, all KASH proteins are drawn as monomers. See text for details.

A similar nuclear migration process in mouse cone photoreceptor development is regulated by SUN1, but the responsible KASH proteins and the involved elements of the cytoskeleton are unknown.<sup>23</sup> The localization at the nuclear periphery of another KASH protein, MSP-300 also depends on klaroid.<sup>24</sup> MSP-300 is an ortholog of mammalian nesprin-1 and -2. Although its role in nuclear anchorage was previously unclear,<sup>24–26</sup> a recent study revealed that MSP-300 interacts with D-Titin/Sallimus and anchors mitochondria and endoplasmic reticulum (ER) to the striated muscle Z-discs.<sup>27</sup> It also cooperatively functions with Klarsicht to promote even nuclear spacing in striated muscle.<sup>27</sup> In *C. elegans*, UNC-84 co-localizes with Ce-lamin at the NE and its localization depends on Ce-lamin.<sup>28</sup> UNC-84 recruits the KASH proteins UNC-83 and ANC-1 to the NE (Fig. 1A).<sup>10,29</sup> UNC-83 in turn targets kinesin-1 and/or dynein to the nuclear periphery, and the force provided by the motor proteins drives the nuclear migration in *C. elegans* hypodermal P cells and embryonic hypodermal cells.<sup>30–32</sup> ANC-1 interacts with F-actin and is required for nuclear anchorage in the adult *C. elegans* syncytial hypodermis.<sup>10</sup>

SUN-KASH complexes can also link chromosomes to the cytoskeleton. In *Schizosaccharomyces pombe*, centromeres are tethered to the SUN protein Sad1 through Csi1 (Fig. 1B).<sup>33</sup> Loss of Sad1 or Csi1 leads to high-frequency centromere clustering defects.<sup>33</sup> At meiotic prophase, telomeres are tethered to Sad1 through Bqt1, Bqt2 and telomere-associated proteins Taz1 and Rap1.<sup>6</sup> Telomeres are further linked to dynein motors by the KASH protein Kms1 and Kms2 (Fig. 1B).<sup>34–37</sup> This results in telomere clustering and later in nuclear oscillation between the cell poles, which facilitates homologous pairing and recombination.<sup>38</sup> In mammals, a recent study revealed the formation of a

similar chromosomal bouquet mediated by a SUN1-KASH5 complex.<sup>7</sup> Table 1 provides an overview of known SUN-KASH pairs from different organisms and their known or proposed functions.

The structure of the mammalian SUN-KASH complex was recently resolved.<sup>39,40</sup> In this complex, three KASH domains are anchored in one cloverleaf-like trimer of SUN domains. The SUN domain protomer has several functional domains: an  $\alpha$ -helical stalk, a compact  $\beta$ -sandwich core, a cation-loop, and a protruding anti-parallel  $\beta$ -sheet named the KASH-lid (Fig. 2). The  $\alpha$ -helix serves as an extension of the trimeric coiled-coil domain of SUN proteins, which facilitates the trimerization. The trimer is further stabilized by a large interacting surface on the  $\beta$ -sandwich core and the hydrogen bonds between the  $\alpha$ -helix of one protomer to the  $\beta$ -sandwich of the adjacent protomer. The KASH domain is clamped between the KASH lid of one protomer and the  $\beta$ -sandwich core of the adjacent protomer. Without binding the KASH domain, the KASH-lid conformation is rather random.<sup>40</sup> The very C-terminal “PPPX” motif is positioned in a KASH pocket formed by S641, Y703, Y707, H628 and the cation-loop (Q593-C601), which explains why these four amino acids are critical for SUN-KASH interactions.<sup>40</sup>

### Nuclear Positioning in Plants

Nuclear positioning events are involved in considerable aspects of the plant life cycle. The most obvious example of nuclear movement is pollen tube growth, during which sperm cells and the vegetative nucleus migrate over long distances toward the tip of the growing pollen tube (for a recent review, see ref. 41). In

**Table 1.** Known SUN-KASH pairs from different organisms, their cytoplasmic partners, and their known or proposed functions

SUN	KASH	Cytoplasmic partner: function	Reference
<b>Mammalian</b>			
SUN1/2	Nesprin-1	F-actin: anchoring the synaptic nuclei under the mouse neuromuscular junction. <sup>18</sup> Dynein/dynactin complex: connecting the nucleus to centrosome for interkinetic nuclear migration and nucleokinesis. <sup>19</sup>	
SUN1/2	Nesprin-2	F-actin: anchoring the synaptic nuclei under the mouse neuromuscular junction. <sup>18</sup> Dynein/dynactin complex and kinesin: connecting the nucleus to centrosome for interkinetic nuclear migration and nucleokinesis. <sup>19</sup>	
SUN1/2	Nesprin-3	Plectin, BPAG1, or MACF: connecting the nucleus to intermediate filaments or microtubules which stabilizes the anchorage of the nucleus and maintains the structure/shape of the nucleus (reviewed in ref. 12).	
Maybe SUN1/2	Nesprin-4	Kinesin-1: predicted to promote nuclear migration toward the base of the secretory epithelial cells. <sup>82</sup>	
SUN1/2	KASH5	Dynein/dynactin complex: telomere movement during meiosis. <sup>7</sup>	
SUN3	Nesprin-1	Proposed to be kinesin II, dynein/dynactin, or F-actin: probably links the nucleus to posterior manchette during sperm head formation. <sup>83</sup>	
SUN1 $\eta$	Nesprin-3	Proposed to be plectin: proposed to be a non-NE complex anchoring acrosome to the anterior actin filaments during sperm head formation. <sup>83</sup>	
SPAG4	Unknown	Unknown: Testis-specific, non-NE localized, function unknown. <sup>84</sup>	
SPAG4L/4L-2	Unknown	Unknown: restricted to the apical nuclear region of round spermatids facing the acrosomic vesicle, and probably involved in linkage of the acrosomic vesicle to the spermatid nucleus and in acrosome biogenesis. <sup>85</sup>	
<b>Drosophila</b>			
Klaroid	MSP-300	F-actin: nuclear anchoring during Drosophila oogenesis. <sup>26</sup>	
Unknown	MSP-300	D-Titin/Sallimus: anchoring mitochondria and endoplasmic reticulum to the striated muscle Z-discs. <sup>27</sup> Unknown: anchoring microtubules to the NE in striated muscle. <sup>27</sup> Unknown: Anchoring the nuclei to myofibril compartment in striated muscle. <sup>27</sup>	
Klaroid	Klarsicht	Proposed to be microtubule motors: nuclear migration during eye development. <sup>20,22</sup>	
Unknown	Klarsicht	Unknown: anchoring microtubules to the NE in striated muscle. <sup>27</sup> Unknown: promoting even myonuclear spacing in both striated muscle and nonstriated myotubes. <sup>27</sup>	
SPAG4/ Giacomo	Unknown	Yuri and dynein/dynactin: involved in centriolar-nuclear attachment during spermatogenesis. <sup>86</sup>	
<b>C. elegans</b>			
UNC-84	ANC-1	F-actin: nuclear anchorage in the adult <i>C. elegans</i> syncytial hypodermis. <sup>10</sup>	
UNC-84	UNC-83	Kinesin-1 and dynein: nuclear migration in embryonic <i>C. elegans</i> hypodermal cells. <sup>30,31</sup>	
SUN-1/matefin	ZYG-12	Dynein and ZYG-12A: linkage between the centrosome and nucleus, <sup>87</sup> meiotic chromosome pairing and synapsis, <sup>88,89</sup> and nuclear positioning within the syncytial gonad. <sup>90</sup>	
SUN-1/matefin	KDP-1	Unknown: cell-cycle progression. <sup>67</sup>	
<b>S. pombe</b>			
Sad1	Kms1 and Kms2	Dynein and centrosomes: meiotic chromosome pairing and synapsis <sup>6,34-37</sup>	
<b>S. cerevisiae</b>			
Mps3	Unknown	Unknown: Mps3 is involved in spindle pole body insertion into the NE and NE homeostasis; <sup>91</sup> it interacts with Mps2 to connect the spindle pole body to the NE and functions in spindle pole body duplication. <sup>92</sup>	
Mps3	Csm4	Probably F-actin: meiotic telomeres are tethered to Mps3 at the NE by Ndj1 and further connected to the cytoskeleton (perhaps actins) by Csm4. <sup>93-95</sup>	
Mps3	Unknown	Unknown: Mitotic telomeres are tethered to Mps3 at the NE by Sir4 and the telomere clustering is mediated by two Mps3 associated proteins, <sup>96</sup> Ebp2 and Rrs1. <sup>97</sup>	
<b>Dictyostelium</b>			
SUN-1	Unknown	Unknown: SUN-1 connects the centrosome to chromatin and ensures genome stability <sup>98</sup>	
Unknown	Interaptin	F-actin: Function unknown <sup>99</sup>	
<b>Arabidopsis</b>			
AtSUN1/2	AtWIP1/2/3	RanGAP: anchoring RanGAP to the NE. <sup>8</sup>	
AtSUN1/2	AtWIP1/2/3	Unknown: nuclear shape determination. <sup>8</sup>	

growing root hairs the nucleus is positioned at a relatively fixed distance from the apex. Interrupting this nuclear positioning by depolymerizing F-actin or trapping the nucleus with a laser beam prohibits root hair growth.<sup>42,43</sup> Similarly, in *Arabidopsis trichomes*—branched, single-cell leaf hairs—the nucleus migrates to a position close to the first branch point.<sup>44</sup>

Asymmetric cell divisions play an important role in plant development. The nucleus has to be positioned at the future division site during this process. During lateral root formation, the nuclei of two neighboring lateral root founder cells migrate toward the common cell boundary. This is followed by asymmetric cell divisions leading to two small adjacent cells and two larger peripheral cells.<sup>45,46</sup> During pollen mitosis I, the nucleus in microspores migrates to allow asymmetric division to produce a large vegetative cell and a small generative cell. *Arabidopsis* microtubule organization 1 (MOR1; also known as GEM1) and its tobacco ortholog tobacco microtubule bundling polypeptide of 200 kDa (TMBP200) are required for this process, and mutations in these proteins lead to defects in pollen production.<sup>47-49</sup> Guard cell formation also involves several steps of asymmetric cell division (reviewed in refs. 50 and 51). In monocots, the guard mother cells arise from one asymmetric division and then divide symmetrically to produce guard cell pairs. Subsequently, the adjacent epidermal cells divide asymmetrically to generate subsidiary cells. In dicots, a protodermal cell divides asymmetrically to produce a meristemoid, which is capable of generating either epidermal pavement cells or guard mother cells.

Nuclear movement is also actively involved in plant-microbe interactions. When arbuscular mycorrhizal fungi penetrate host root cells, the host cell nucleus rapidly positions itself beneath the appressorium contact site and promotes cytoskeleton and ER rearrangements.<sup>52,53</sup> The nucleus then migrates away from the contact site, accompanied by a formation of a column comprised of cytoskeleton and ER.<sup>52,53</sup> This newly formed structure strictly defines the future intracellular path of hyphal penetration and is called the pre-penetration apparatus.<sup>52,53</sup> However, in case of a pathogenic fungus, the host cell nucleus stays at the appressorium contact site accompanied by cell wall thickening and papilla formation that blocks the fungal penetration.<sup>54</sup>

### Plant Meiotic Telomere Movement

Similar to mammalian telomere organization, plant telomeres are also attached to the NE during meiosis.<sup>55,56</sup> During maize (*Zea mays* L.) meiotic prophase I, starting at the end of leptotene, telomeres begin to cluster at the nuclear periphery to form a bouquet.<sup>57</sup> This process persists through zygotene and ends at early pachytene when telomeres start to disperse at the nuclear periphery.<sup>57</sup> In *Arabidopsis*, telomeres move to the nuclear periphery and form a loose cluster, perhaps a temporary bouquet.<sup>58</sup>

Despite the importance of nuclear positioning and chromosome movement during the plant life cycle, little is known about the molecular players involved. The recent identification of NE-bridging complexes in plants has now provided tools to begin investigating the underlying molecular mechanisms.

### Plant SUN Proteins

Two types of SUN protein have been identified in plant genomes: the canonical C-terminal SUN domain (CCSD) type and the plant-prevalent mid-SUN 3 transmembrane (PM3) type.<sup>59,60</sup> The CCSD type has a SUN domain at the C-terminus, while the signature of the PM3 type is a centrally positioned SUN domain followed by a highly conserved domain of unknown function.<sup>60</sup> The PM3 type was first discovered in maize, but is also present in other plant species, as well as in opisthokonts.<sup>60</sup> PM3-type SUN proteins have not yet been functionally investigated. To date, all well-studied SUN proteins belong to the CCSD type, and therefore, only plant CCSD-type SUN proteins will be discussed in detail here.

The *Arabidopsis* genome encodes two CCSD-type SUN proteins—AtSUN1 and AtSUN2.<sup>59,61</sup> They share a similar domain organization with non-plant SUN proteins: an N-terminal domain with a nuclear localization signal (NLS), a transmembrane domain, a coiled-coil domain, and a SUN domain. Deleting the N-terminal domain, the NLS, or the coiled-coil domain of AtSUN1 or AtSUN2 affects their NE localization, suggesting that these domains are involved in NE targeting and integration. Both genes are expressed ubiquitously in various tissues, including roots, hypocotyl, cotyledons, and leaves. As analyzed by fluorescence resonance energy transfer assays, AtSUN1 and AtSUN2 can form homo- or hetero-complexes,<sup>59</sup> perhaps similar to the mammalian SUN protein trimers.

This is supported by the predicted 3D structure of the AtSUN1 SUN domain derived from comparative modeling with the SUN domain of *Homo sapiens* SUN2 (HsSUN2) as a template (Fig. 2A). According to the HsSUN2 model, the SUN2 trimer harbors three binding site for the KASH domain, such that the SUN-KASH complex is a hexamer.<sup>40</sup> AtSUN1 likely harbors the same binding configuration, because the essential structures and amino acids involved in KASH binding are mostly conserved (Figs. 2B and 3): (1) the KASH-binding pocket is very well-conserved; (2) the cation loop is conserved, especially within plant SUN domains; (3) although the residues of the KASH lid are not conserved, a corresponding fragment is present in all plant SUN domains (Fig. 3). In contrast, the residues that are dispensable for SUN-KASH interaction—residue C563 of HsSUN2 that forms a disulfide bond with a cysteine in the KASH domain and residue N636 of HsSUN2, the N-glycosylation site—are not conserved in plant SUN domains (Fig. 3).

**Plant ONM SUN-binding proteins.** Although the sequences and the KASH binding features are conserved between mammalian and plant SUN domains, plant genomes do not encode any homologs of opisthokont KASH proteins.

WPP domain-interacting proteins (WIPs) are plant tail-anchored ONM proteins that contain a cytoplasmic coiled-coil domain, a transmembrane domain, and a PNS tail terminated in a conserved “VPT” motif. WIPs are plant-specific proteins and *Arabidopsis* has three homologs—AtWIP1, AtWIP2, and AtWIP3. They are redundantly involved in anchoring the Ran GTPase activating protein (RanGAP) to the NE. This anchorage is achieved by the interaction between the N-terminal plant-specific



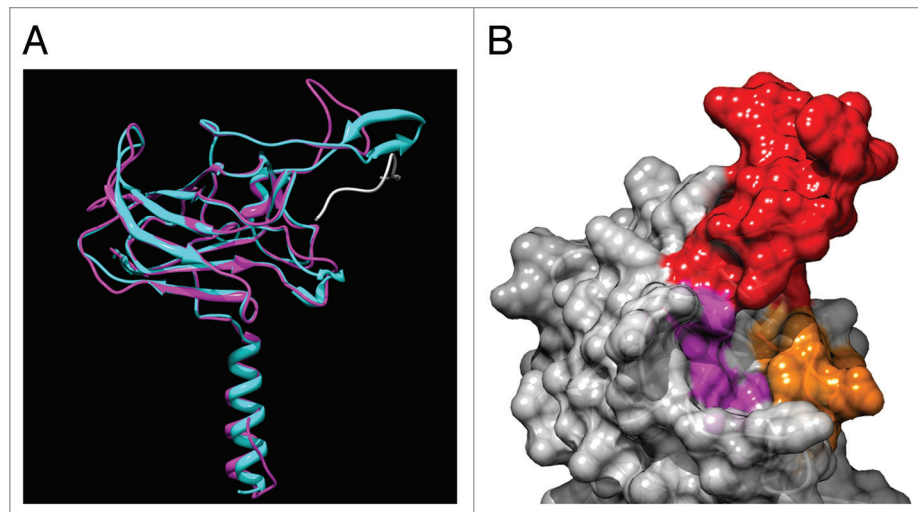
WPP domain of RanGAP and the coiled-coil domain of WIPs. A combination of immunofluorescence and immunogold-labeling experiments showed that WIPs are associated with the ONM.<sup>62,63</sup>

A combination of co-immunoprecipitation and fluorescence recovery after photobleaching experiments demonstrated that AtWIP1, AtWIP2, and AtWIP3 interact with AtSUN1 and AtSUN2 at the plant NE.<sup>8</sup> The PNS tail of AtWIP1, especially the “VPT” motif, is required for the interaction, similar to the interactions between mammalian Nesprins and SUNs.<sup>4,16,64</sup> Surprisingly, the PNS tail of WIP1 is only 9 amino acids long. The PNS tail of *Homo sapiens* Nesprin-2 is 30 amino acids long, and its C-terminal fragment of 14 amino acids is the shortest one able to bind the SUN domain.<sup>40</sup> The ability of Arabidopsis SUN proteins to bind a very short PNS tail might be connected to the presence of a stretch of additional conserved residues in plant SUN domains,<sup>8</sup> however, further work is required to understand the exact biochemical nature of the unusual plant NE-bridging complex.

### Function of the AtSUN-AtWIP Complex in RanGAP NE Anchoring

The NE localization of AtWIP1 is reduced in a *sun1-knockout sun2-knockdown* (*sun1-KO sun2-KD*) mutant, suggesting that the localization of AtWIPs depends on AtSUNs, analogous to the animal KASH proteins.<sup>8</sup> Consistent with these findings, the NE localization of AtRanGAP1 is also reduced in undifferentiated root cells of the *sun1-KO sun2-KD* mutant, indicating that plant SUN proteins play a role in RanGAP-NE association by forming a RanGAP-WIP-SUN complex. The existence of this complex is supported by co-immunoprecipitation data.<sup>8</sup>

AtRanGAP1 is currently the only confirmed cytoplasmic partner of an NE-bridging complex that does not appear to be associated with elements of the cytoskeleton. RanGAP is the GTPase activating protein for the small GTPase Ran. RanGTP hydrolysis is an important step in nucleocytoplasmic trafficking and implied in the release of cargo from export receptors after exiting from the



**Figure 2.** Computed three-dimensional model of the SUN domain of AtSUN1. (A) The S251-D453 fragment of AtSUN1 was modeled using MODELER.<sup>79</sup> The SUN domain of HsSUN2 was used as a template (PDB: 4FI9). Three models were computed and the one with the lowest zDOPE score is shown. Magenta, model of the AtSUN1 SUN domain. Cyan, SUN domain of HsSUN2. Gray, Nesprin-2 KASH domain in the HsSUN2-KASH complex. (B) Computed surface of the binding pocket for the KASH C-terminus in AtSUN1. Red, V301-N318 fragment of AtSUN1 corresponding to the KASH lid of HsSUN2 (Y567-S587). Orange, S324-C333 fragment of AtSUN1, corresponding to the cation-loop of HsSUN2 (Q593-C601). Purple, residue H360, S371, H439, and Y443 of AtSUN1, corresponding to H628, S641, Y703, Y707 of HsSUN2, respectively. Images were generated using UCSF Chimera package<sup>80</sup> and POV-Ray (<http://www.povray.org/>).

nuclear pore at the cytoplasmic surface.<sup>65</sup> Both metazoan and plant RanGAP is associated with the outer NE, but the mechanisms differ. The RanGAP-WIP-SUN complex appears to be specific for plants. Mammalian nuclear pore-associated RanGAP1 is in a complex containing the SUMO E3-ligase nucleoporin RanBP2, SUMOylated RanGAP1 and the E2 SUMO-conjugating enzyme UBC9.<sup>66</sup> The finding that plants have recruited an NE-bridging complex to anchor RanGAP to the NE suggests that there may be additional functions for such complexes beyond linking the nucleus and the cytoskeleton. Thus, novel, cytoskeleton-unrelated binding partners might also exist for opisthokont KASH proteins. One such KASH protein candidate might be *C. elegans* KDP-1, which functions in cell cycle progression from late S to M phase, and for which a cytoplasmic partner is currently unknown.<sup>67</sup>

### Function of the AtSUN-AtWIP Complex in Nuclear Shape Determination

It is possible that WIPs additionally interact with motor proteins or the cytoskeleton. However, neither the *wip1-1 wip2-1*

**Figure 3 (See opposite page).** Amino acid sequence alignment of plant SUN domains with the SUN domain of HsSUN2. Alignment was performed using ClustalW2 (<http://www.ebi.ac.uk/Tools/msa/clustalw2/>) with default settings, except that the output sequences were kept as input order. Image was generated using JalView<sup>81</sup> and ClustalX color. GI, NCBI GenInfo identifier. Black frames in the alignment are numbered at the top. Frame 1 indicates C563 in HsSUN2, which forms a disulfide bond with *Homo sapiens* Nesprin-2 C6862. This disulfide bond is dispensable for SUN-KASH interaction, and in plant SUN domains this position is instead a conserved D or E. Frame 2 indicates the KASH-lid in HsSUN2, however, the sequences have low similarity between HsSUN2 and plant SUN proteins. Frame 3 represents the cation loop in HsSUN2. This cation loop and residues indicated by frame 4, 6, 7, 8 (correspond to H628, S641, Y703, and Y707 of HsSUN2, respectively) form the pocket holding the KASH C-terminus and are well conserved in plant SUN domains. Frame 5 represents N636 of HsSUN2, the N-glycosylation site. N-glycosylation of HsSUN2 is dispensable for KASH binding, and this position is a conserved D in plant SUN domains.



HsSUN2_GI29337242	1	-----VTEEQVHHIVKQALQRYSEDRIGLADYALESGGASVISTROSETYETKTALLSLFCIP-----LWYHSQSP	66
AtSUN1_GI15238380	1	SEISIDELRAYARDIMEKEIEKHAADGLGRVDYALASGGAFVMEHSDPYLVGKGSSWFATTMR-----RAHTNA	69
AtSUN2_GI30681463	1	SDVNIDKLRAYARDIVEKEIGKHVADGLGRVDYALASGGAFVMEHSDPYLVGKGSSWFATTMR-----RVHKA	69
Ricinus_GI255564800	1	TGVSLLDIRLAYAKEIVIKEIEKHAADGLGMVDYALASGGAIVVKHSEFLLPGKGTMLLKSSR-----IGVHPDA	70
Grape_GI225463743	1	REMSLDEIRGAREIVEKEIERHAADGLGRVDYALSSSGAMVVRHSEPIYILKGSGWFPKTSL-----TGVRHDS	70
Poplar_GI224110050	1	SDVSLDDIMVYAREIVQKEIEKHAADGLGRVDYALATSGGMVVKHSDPYMAGRGVMWFLKGR-----GVHPNA	68
Poplar_GI224097492	1	SGVGLDDIMAYAREIVQKEIDKHAADGLGRVDYALATSGGMVVKHSDPYMAVRGANWFMKGG-----GVHPNA	68
Sorghum_GI242064200	1	DEISLDDIRLYAKEVVEMEIAHRSADGLGMVDYALSGGAKVVSHPFMNG--KNYLPGRS-----VHTTA	66
Maize_GI226509595	1	DEISLDDIRLYAKDVVEMEIAHRSADGLGMVDYALSGGAKVVSHPFMNG--KNYLPGRSN-----VHTTA	66
Rice_GI115462915	1	GDISLDDIRLFAKEIVEMEIERHAADGLGMVDYALASGGGKVVKHSEAFRKA--KSFMPSRNS-----LLECA	66
Rice_GI115435856	1	TEVDLDQVRALAREITMGEIEKHAADGIRVDYAVASAGGKVVVRHSDAYDAGKRGGFFSSLLS-----GDTAASP	70
Maize_GI195640474	1	SEVDLDQVRALAREIVMREIEKHAADGIRVDYAVASGGGRVVRHSEAYVP--KRG-FMWMSG-----VDVGPKP	68
Lycophyte_GI302820579	1	KSLTLDDVRIARQIVEAELEKHSADGIRVDYALSGGGKIEHSEGGFTTGGRAGWLSILGAGLSAGGAVRHPMA	76
Lycophyte_GI302824915	1	KSLTLDDVRIARQIVEAELEKHSADGIRVDYALSGGGKIEHSEGGFTTGGRAGWLSILGAGLSAGGAVRHPMA	76
Lycophyte_GI302762370	1	KALISLDDVRAAARKVVGSELETHAADGIRVDFALESGGGKVVHSDGYFQG---LHWTRLGIHVLPGVFRRHPMA	73
Lycophyte_GI302814206	1	KALISLDDVRAAARKVVGSELETHAADGIRVDFALESGGGKVVHSDGYFQG---LHWTRLGIHVLPGVFRRHPMA	73
Lycophyte_GI302774312	1	KALISLDDVRAAARKIIEDELERHRADGIRTDYALASGGGRVIDYSEGYFS--LTPWSGLLG--ILPGDYRRHPKA	72
Lycophyte_GI302769986	1	KALISLDDVRAAARKIIEDELERHRADGIRTDYALASGGGRVIDYSEGYFS--LTPWSGLLG--ILPGDYRRHPKA	72
Moss_GI168048151	1	KSFSLDVDRSIARKIVMSEVEKHAADGIRTDYALASGGGRVVDHSEGVFLGRGRQLFSMVFS--LTGEARKHPLA	76
Moss_GI168011079	1	KSFSLDVDRSVARKIVMSELEKHAADGIRTDYALASGGGRVVDHSEGVFLGRGQQVSLMFGHIVPGGTRKHPLA	76
HsSUN2_GI29337242	67	RVILQPDVHP-GNOWAFQGFQGFVAVRLSARIRPTAVTLEHVPKALSPASTISSAPKDFAIFFGFDLQOEG----	137
AtSUN1_GI15238380	70	VKMLSPSFGEPGQCFPLKGSSEGYVQIRLRGPIPEAVTLEHVAKSVAAYD--RSSAPKDCRVSGSLQGP--ESSAET	141
AtSUN2_GI30681463	70	VKMLTPSFGEPGQCFPLKGSNGYVLRRLAPIPEAVTLEHVAKSVAAYD--RSSAPKDCRVSGSLQGP--DIDMET	139
Ricinus_GI255564800	71	VKMLKPSFGEPGQCFPLKGSSEGYVQIRLRGPIPEAVTLEHVAKSVAAYD--RSSAPKDCRVSGSLQGP--DIDMET	144
Grape_GI225463743	71	EKMLKPSFGEPGQCFPLKGSSEGYVQIRLRGPIPEAVTLEHVAKSVAAYD--RSSAPKDCRVSGSLQGP--DIDMET	144
Poplar_GI224110050	69	DEMLKPSFGEPGQCFPLKGSSEGYVQIRLRGPIPEAVTLEHVAKSVAAYD--RSSAPKDCRVSGSLQGP--DIDMET	142
Poplar_GI224097492	69	DEMLKPSFGEPGQCFPLKGSSEGYVQIRLRGPIPEAVTLEHVAKSVAAYD--RSSAPKDCRVSGSLQGP--DIDMET	142
Sorghum_GI242064200	67	QKMLEPSFGQPGCEFAVKGSSGFVVKVLRRTAIPPEAVTLEHVDKSVAYD--RSSAPKDFQVRGAYQGHDDSEKDS	140
Maize_GI226509595	67	QKMLEPSFGQPGCEFAVKGSSGFVVKVLRRTAIPPEAVTLEHVDKSVAYD--RSSAPKDFQVRGAYQGHDDSEKDS	140
Rice_GI115462915	67	KKMLEPSFGQPGCEFAVKGSSGFVVKVLRRTAIPPEAVTLEHVDKSVAYD--RSSAPKDFQVRGAYQGHDDSEKDS	140
Rice_GI115435856	71	KKILQPSFGEPGQCFPLKGSSEGYVQIRLRGPIPEAVTLEHVAKSVAAYD--RSSAPKDCRVSGSLQGP--DIDMET	144
Maize_GI195640474	69	EKMLKPSFGEPGQCFPLKGSSEGYVQIRLRGPIPEAVTLEHVAKSVAAYD--RSSAPKDCRVSGSLQGP--DIDMET	142
Lycophyte_GI302820579	77	HKVLEPSYGEFGQCLPLKGSNVFVEIALRTHIHDPDAITIEHVPKSVAYD--VTSAPKDFRVFGWALERSIQAGT	150
Lycophyte_GI302824915	77	HKVLEPSYGEFGQCLPLKGSNVFVEIALRTHIHDPDAITIEHVPKSVAYD--VTSAPKDFRVFGWALERSIQAGT	150
Lycophyte_GI302762370	74	DRLLRPSFGEPGQCLPLKGSNVFVEIALRTHIHDPDAITIEHVPKSVAYD--VTSAPKDFRVFGWALERSIQAGT	144
Lycophyte_GI302814206	74	DRLLRPSFGEPGQCLPLKGSNVFVEIALRTHIHDPDAITIEHVPKSVAYD--VTSAPKDFRVFGWALERSIQAGT	144
Lycophyte_GI302774312	73	NKILEPSFGEPGQCLPLKGSNVFVDILRRTAIYADSIIEHVPKSVAYD--VTSAPKDFRVFGWALERSIQAGT	142
Lycophyte_GI302769986	73	NKILEPSFGEPGQCLPLKGSNVFVDILRRTAIYADSIIEHVPKSVAYD--VTSAPKDFRVFGWALERSIQAGT	142
Moss_GI168048151	77	QKMLEPSFGEPGQCLPLKGSNVFVEIALRTHIHDPDAITIEHVPKSVAYD--VTSAPKDFRVFGWALERSIQAGT	150
Moss_GI168011079	77	QKMLEPSFGEPGQCLPLKGSNVFVEIALRTHIHDPDAITIEHVPKSVAYD--VTSAPKDFRVFGWALERSIQAGT	150
HsSUN2_GI29337242	138	-----TLLGKFTYDQDG-EPIQTFFHQ--APTAMATYQVVELRLITNWGHPEYTCIMRFRVHGEPAH	195
AtSUN1_GI15238380	142	EN---MQLLTFEFTYDLDR-SNAQTFNFI-ESSSSGLIDTVRLDFTSNHGSSTHTCIMRFRVHGGRAPD	203
AtSUN2_GI30681463	140	ET---MPLLTFEFTYDLDR-SNAQTFNFI-DSAHSGLVNIVRLDFTSNHGSSTHTCIMRFRVHGRELD	201
Ricinus_GI255564800	145	EK---MFLLTFTYDLEK-SNAQTFNFI-NSVASGLVDIVRLDFTSNHGSSTHTCIMRFRVHGREPD	206
Grape_GI225463743	145	GS---MFLLAETFTYDLEK-SNAQTFNFI-DLVGSGLVDMVRFDFTSNHGSSTHTCIMRFRVHGHELD	206
Poplar_GI224110050	143	EK---MFLLTFTYDLEK-SNAQTFNFI-DNTASGLVDIVRLDFTSNHGSSTHTCIMRFRVHGREPD	204
Poplar_GI224097492	143	EK---MFLLTFTYDLEK-SNAQTFNFI-DKTASGLVDIVRLDFTSNHGSSTHTCIMRFRVHGREPD	204
Sorghum_GI242064200	141	NV---MAALGEFSYDLDK-SNAQTFQLE-RTADSRVNMVQLDFSSNHGNLELTCIMRFRVHGREPG	202
Maize_GI226509595	141	NV---MSTLGEFSYDLDK-SNAQTFQLE-RTAQSRVNMVQLDFSSNHGNLELTCIMRFRVHGRKPV	202
Rice_GI115462915	141	RV---VTNLGEFSYDLDK-SNAQTFQLE-RTADSRVINMVRDLDFSSNHGNLELTCIMRFRVHGREPG	202
Rice_GI115435856	145	AASAKMYVLTFEFTYDLDK-KNVQTFDIT-AP-DVGIINMVRDLDFSSNHGSSTHTCIMRFRVHGHPEV	208
Maize_GI195640474	143	AA---KMALAEFAYDLEK-KNVQTFDIT-AP-DVGINMVRDLDFSSNHGSSTHTCIMRFRVHGHPEV	203
Lycophyte_GI302820579	151	PVK---KLLLGEFSYSLDG-SNIQTFSFP-EEVSRELINTVRIHITSNHGSSTHTCIMRFRVHGHGEP	213
Lycophyte_GI302824915	151	PVK---KLLLGEFSYSLDG-SNIQTFSFP-EEVSRELINTVRIHITSNHGSSTHTCIMRFRVHGHGEP	213
Lycophyte_GI302762370	145	ARN---VTSLGRFTYDLEK-GSIQTFDLS-DKPTSS-VNMIHLVLSNYGSPHTCIMRFRVHGHGEP	202
Lycophyte_GI302774312	143	KGE---RVLLGSFRYDIES-SSVQTFRLY-KTASKLLVNTVRVHVSNYGSSTHTCIMRFRVHGHGEP	205
Lycophyte_GI302769986	143	KGE---RVLLGSFRYDIES-SSVQTFRLY-KTASKLLVNTVRVHVSNYGSSTHTCIMRFRVHGHGEP	205
Moss_GI168048151	151	SPV---HRLLGQFVYKTDGPNISQITFHLSEKEDVGDEPINMVRDLDFSSNHGSSTHTCIMRFRVHGVDPQ	215
Moss_GI168011079	151	SPE---HKLGGQFIYNSDGSNVQTFQLSKDDVGDEPINMVRDLDFSSNHGSSTHTCIMRFRVHGVDPQ	215

Figure 3. For figure legend, see page 210.

*wip3-1* nor the *sun1-KO sun2-KD* mutant has obvious defects in nuclear positioning or plant development.<sup>8,61</sup> The only phenotype observed in these mutants was a reduced nuclear polarity in root hairs, leaf epidermal cells, and trichomes.<sup>8,61</sup> In wild-type

Arabidopsis root hair cells, trichomes, and some of the leaf epidermal cells, the nucleus is spindle-shaped.<sup>8</sup> Especially in root hair cells, the super-elongated nucleus resembles a “pod” with two thin tails attached to its poles.<sup>8</sup> In the *wip1-1 wip2-1 wip3-1*

mutant or the *sun1-KO sun2-KD* mutant, this spindle shape is lost, indicating that both WIP and SUN are required for maintaining an elongated nuclear structure in these cell types.<sup>8</sup> It is possible that an unknown factor anchored by the SUN-WIP complex regulates the nuclear shape in the *Arabidopsis* epidermis (Fig. 1C, indicated by the oval with a question mark).

Intriguingly, loss-of-function mutants of two *Arabidopsis* nuclear long coiled-coil proteins, LITTLE NUCLEI 1 and 2 (LINC1 and LINC2; recently renamed to CROWDED NUCLEI 1 [CRWN1] and 2 [CRWN2] to avoid confusion with the LINC complex), also lead to the loss of nuclear elongation, in addition to a reduced nuclear size.<sup>68</sup> Plant genomes do not encode homologs of animal lamin genes. The *Daucus carota* L. (carrot) nuclear matrix constituent protein 1 (NMCP1) and its *Arabidopsis* homologs—CRWN1, CRWN2, CRWN3 and CRWN4—have been proposed as putative plant counterparts of animal lamins. They are conserved in many plant species and contain long coiled-coil domains similar to lamins, though at almost twice the size, and NMCP1 and CRWN1 are located at the nuclear periphery.<sup>68,69</sup> In addition to the nuclear shape change, the *crwn1-1 crwn2-1* double mutant has a significantly reduced nuclear volume, fewer chromocenters, and a dwarf plant phenotype.<sup>68</sup>

Nuclear shape change caused by mutations in lamin genes was observed in a series of human diseases called laminopathies.<sup>70</sup> One such disease is Hutchinson–Gilford progeria syndrome (HGPS), which is linked to point mutations in the human lamin A gene (*Lmna*). Patients suffer from a series of premature-aging symptoms—among others, loss of hair, restrictive joint mobility, and cardiovascular disease. One of the hallmarks of HGPS cells is the occurrence of blebbed and lobulated nuclei.<sup>71</sup> This defect of nuclear shape is reversely proportional to the amount of nesprin-2 at the NE,<sup>72</sup> and mutation or silencing of nesprin-2 also causes blebbed nuclei in both mouse and human cells.<sup>73</sup> Unexpectedly, the mutation of SUN1 in *Lmna*<sup>-/-</sup> mice did not accelerate the pathological phenotypes, but instead ameliorated them and corrected the nuclear aberrancies in fibroblasts.<sup>74</sup> In light of the SUN1 overaccumulation observed in *Lmna*<sup>-/-</sup> cells, this implies SUN1 overabundance as a pathogenic event in HGPS and a trigger of nuclear shape aberrancies.

The involvement of both lamins and lamin-like proteins and SUN-KASH complexes in nuclear shape in both plants and mammals and their connection to human disease make it worthwhile to further investigate the biological relevance of nuclear morphology at the cellular and organismal level.

### Possible Function of Plant SUN Proteins in Mitosis and Meiosis

Mammalian SUN1 is associated with NPCs and interacts with lamins.<sup>75</sup> It is suggested that this kind of INM protein links

mitotic ER to chromatin in telophase and might mediate NE reassembly during mitosis.<sup>76</sup> A similar mechanism might also exist in plants. In *Arabidopsis*, AtSUN1 diffuses to the ER after NE breakdown and is mainly located at the distal side of the separated chromosomes throughout anaphase.<sup>61</sup> At telophase, an enriched AtSUN1 signal starts to enclose the chromosomes from the distal surface to the proximal surface. At the same time, the signal at the ER becomes gradually reduced, indicating the translocation of AtSUN1 to the newly formed NE.<sup>61</sup> Studies of AtSUN1 and AtSUN2 in BY-2 cells showed similar results.<sup>77</sup> Additional work using BY-2 cells also showed that AtSUN1 and AtSUN2 are associated with membranes around the spindle and close to the chromosomes.<sup>77</sup>

During plant meiotic prophase I, the telomere bouquet associated with the NE has roles in interhomolog pairing, synapsis, and homologous recombination. Evidence for a possible involvement of plant SUN proteins in this process comes from the maize desynaptic (*dy*) mutant.<sup>78</sup> This mutant is defective in chromosome synapsis, recombination, telomere-NE tethering, and chromosome segregation. Linkage mapping combined with a candidate-gene approach make it likely that a splice variant of maize SUN3 is responsible for this phenotype.<sup>78</sup>

### Perspectives

Our understanding of the nature and role of plant NE proteins has just begun. Compared with the nuclear pore proteins, NE proteins appear to be even less conserved between plants and animals. This suggests that the hunt for plant NE proteins largely will be by de novo identification, rather than homology searches. It is exciting to learn that NE-bridging complexes are conserved in plants and that they perform plant-specific functions through plant-specific ONM partners. A cornucopia of new questions follows from these findings: How is the SUN-WIP complex involved in the developmental changes in nuclear morphology? Are there additional plant NE-bridging complexes and are they connected to the cytoskeleton? Are they involved in nuclear migration? Do plant SUN proteins interact with other IMN proteins and do they interact with a plant lamina? How are plant SUN proteins involved in chromosomal positioning? Perhaps the answers to these questions will help resolve a more general enigma: why is the complement of NE proteins so different in plants? And what does this tell us about the separate evolution of NE functions in plants and opisthokonts? A rapid resolution of these questions is unlikely, but their answers will certainly lead to a broader, more comparative understanding of the physical interaction of the nucleus with its cellular environment.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.



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